Neuronal histamine and expression of corticotropin-releasing hormone, vasopressin and oxytocin in the hypothalamus: relative importance of H₁ and H₂ receptors

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Abstract

Centrally administered histamine (HA) stimulates the secretion of the pro-opiomelanocortin-derived peptides ACTH and β -endorphin as well as prolactin. The effect of HA on secretion of these adenohipophysial hormones is indirect and may involve activation of hypothalamic neurons containing corticotropin-releasing hormone (CRH), arginine-vasopressin (AVP) or oxytocin (OT).

We studied the effect of activating central HA receptors by central infusion of HA, HA agonists or antagonists on expression of CRH, AVP and OT mRNA in the hypothalamic paraventricular (PVN) and supraoptic (SON) nuclei.

Intracerebroventricular infusion of HA (270 nmol), the H₁-receptor agonist 2-thiazolyethylamine or the H₂-receptor agonist 4-methylhistamine increased the level of CRH mRNA in the PVN, and OT mRNA in the SON. In contrast, none of these compounds had any effect on expression of AVP mRNA in the PVN or SON. Administration of the H₁-receptor antagonist mepyramine or the H₂-receptor antagonist cimetidine had no effect on basal expression of CRH, AVP or OT mRNA in the PVN and/or SON except for a slight inhibitory effect of cimetidine on CRH mRNA expression in the PVN. Pretreatment with mepyramine or cimetidine before HA administration inhibited the HA-induced increase in OT mRNA levels but had no effect on the HA-induced increase in CRH mRNA levels in the PVN.

We conclude that HA stimulates hypothalamic CRH and OT neurons by increasing mRNA levels, and this effect seems to be mediated via activation of both HA H₁ and H₂ receptors.

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Introduction

Histamine (HA), which acts as a hypothalamic neurotransmitter (1), participates in the central regulation of anterior pituitary hormone secretion and stimulates secretion of the pro-opiomelanocortin-derived peptides adrenocorticotropin (ACTH) and β -endorphin as well as prolactin (2). Furthermore, histaminergic neurons, which originate exclusively in the posterior hypothalamus (1), seem to be involved in the mediation of stress-induced release of these hormones (2). Since HA does not appear to stimulate ACTH/ β -endorphin (3, 4) or prolactin secretion (5, 6) directly at the pituitary level, its action may be indirect via activation of hypothalamic neurons, which subsequently release hypophysiotropic factors which stimulate pituitary hormone secretion. Corticotropin-releasing hormone (CRH) as well as arginine-vasopressin (AVP) and oxytocin (OT) are involved in regulation of ACTH and β -endorphin (7, 8) secretion, and AVP and OT are also involved in control of prolactin secretion (9). Therefore activation of CRH-, AVP- and OT-containing neurons may be essential for the HA-induced release of pituitary

hormones. In accordance with this hypothesis, hypothalamic nuclei, including the paraventricular nucleus (PVN) and the supraoptic nucleus (SON), which contain CRH, AVP and OT neurons (10), are innervated by histaminergic fibers (11, 12), which thereby provide the anatomical basis for a functional interrelation between histaminergic neurons and CRH, AVP and OT neurons. Furthermore, we have recently found that centrally administered HA stimulates the expression of *c-fos* in hypothalamic CRH, AVP and OT neurons (13) and the formation of CRH, AVP and OT mRNA in the hypothalamus (14), suggesting that these neurons are activated by HA. Finally, we have shown that centrally administered HA releases AVP and OT into peripheral plasma (15) and CRH into pituitary portal blood (16). These findings also support our previous finding that HA is an important regulator of AVP and OT as peripheral hormones since histaminergic blockade inhibits dehydration-induced AVP secretion (17) and suckling-induced OT secretion (18).

The aim of the present study was to characterize histaminergic activation of hypothalamic CRH, AVP

and OT neurons further, with special emphasis on the type of postsynaptic HA receptor involved. To do so, we studied the effect of centrally administered HA, HA agonists and HA antagonists on the levels of mRNA for CRH, AVP and OT in the PVN and SON in conscious male rats.

Materials and methods

Animals

Male rats of the Wistar strain (275–325 g) bred at the Panum Institute were housed under controlled conditions of temperature (22 °C), relative humidity (45–50%) and lighting (lights on between 0600–1800 h daily). The rats had free access to laboratory chow and tap water.

Compounds

The compounds used were HA dihydrochloride (molecular weight of HA, 111; Sigma Chemicals, St Louis, MO, USA), the H₁-receptor agonist 2-thiazolyethylamine (2-TEA; molecular weight 128; gift from Smith, Kline & Beecham, Welwyn Garden City, Herts, UK) (19), the H₂-receptor agonist 4-methylhistamine (4-MeHA; molecular weight 126; gift from Smith, Kline & Beecham) (19), the H₁-receptor antagonist mepyramine (MEP; molecular weight 286; gift from DAK Laboratories, Copenhagen, Denmark) (19), and the H₂-receptor antagonist cimetidine (CIM; molecular weight 252; gift from Smith, Kline & Beecham) (19).

Surgical and experimental procedures

At 5–7 days before experimentation, a permanent metal cannula was implanted into the right lateral ventricle of the brain of all rats for i.c.v. infusions. The cannula was positioned as previously described (coordinates 1.5 mm lateral from the bregma on the coronal suture, 4.5 mm below the surface of the skull) (20). Implantation was performed during pentobarbital anesthesia (60 mg/kg i.p.).

All experiments were performed in conscious freely moving rats and between 1000 and 1200 h. On the day of experimentation the i.c.v. cannulas were extended by silastic tubing and the rats were left undisturbed in individual cages in a quiet room for an adaptation period of at least 90 min.

Experiment 1: effect of HA or selective H₁- or H₂-receptor activation on CRH, AVP and OT mRNA in the hypothalamic PVN and SON

HA (270 nmol), the H₁-receptor agonist 2-TEA (2180 nmol), the H₂-receptor agonist 4-MeHA (790 nmol) or saline (control) was infused i.c.v. (5 µl; 2 µl/min) at

–240 min. The dose of HA was chosen to stimulate significantly but submaximally the secretion of ACTH, β-endorphin (21) and prolactin (22). This dose was previously shown to be able to stimulate neuropeptide mRNA levels (14). The doses of 2-TEA and 4-MeHA were chosen to be equipotent to the HA dose with respect to ACTH release (23).

At time 0 min, the rats were decapitated, and brains were rapidly removed, frozen on dry ice and stored at –80 °C. The 240 min period between stimulation and decapitation was chosen as it has previously been shown to be optimal for demonstrating stress-induced changes in CRH mRNA (24). Sections (12 µm) were prepared as previously described (13). Synthetic DNA oligonucleotide probes directed against rat CRH bases 496–543 (25), AVP bases coding for the N-terminal 16 amino acids of the glycopeptide sequence (26), and OT bases 247–294 (26) were used for *in situ* hybridization. The probes were labeled and hybridization and exposure performed as previously described (13). The exposure times were 3 weeks, 1 day and 2 days for CRH, AVP and OT mRNA respectively. X-ray autoradiograms were quantified using a computer-assisted image analysis system (Image 1.49; Wayne Rasband, NIH, Bethesda, MD, USA), and no attempts to differentiate between subdivisions of the PVN and SON were made. Direct comparison of the effect of histaminergic compounds on neuropeptide mRNA levels between different brain areas was made easier by arbitrarily setting hybridization levels in control animals as 100. Background values from neighboring areas considered to be free of positive hybridization were subtracted from individual sections, thus serving as their own background control.

Experiment 2: effect of selective H₁- or H₂-receptor blockade on basal and HA-induced CRH, AVP and OT mRNA in the hypothalamic PVN and SON

Rats were pretreated with i.c.v. infusion (5 µl; 2 µl/min) of the H₁-receptor antagonist MEP (350 nmol), the H₂-receptor antagonist CIM (400 nmol) or saline (control) at –245 min. After 5 min, HA (270 nmol) or saline (control) was infused i.c.v. (5 µl; 2 µl/min) at time –240 min.

At time 0 min, the rats were decapitated and their brains rapidly removed and treated as described for experiment 1.

Statistical analysis

Data are presented as the mean ± S.E.M. for five to eight rats. Comparison of the mRNA levels between treatment groups was performed by a one-way ANOVA followed by Duncan's procedure for multiple comparisons where appropriate. *P* < 0.05 was considered significant.

Figure 1 Effect of HA, HA agonists or HA antagonists on CRH mRNA in the PVN. Rats were pretreated at time -245 min with an i.c.v. infusion of the H_1 -receptor antagonist MEP, the H_2 -receptor antagonist CIM or saline (Sa; control). After 5 min, HA, the H_1 -receptor agonist 2-TEA, the H_2 -receptor agonist 4-MeHA or saline (control) was administered. At time 0 min, rats were decapitated and *in situ* hybridization histochemical analysis of CRH mRNA was performed. The data represent means $\pm$ s.e.m. for five to eight animals. * $P < 0.05$; ** $P < 0.01$ vs Sa + Sa.

Results

Experiment 1: effect of HA or selective H_1 - or H_2 -receptor activation on CRH, AVP and OT mRNA in the hypothalamic PVN and SON

Central administration of HA, the H_1 -receptor agonist 2-TEA or the H_2 -receptor agonist 4-MeHA increased CRH mRNA levels in the PVN by 10% to 25% (Fig. 1; $P < 0.05/P < 0.01$).

The levels of AVP mRNA in both the PVN and SON were unaffected by infusion of HA, 2-TEA or 4-MeHA (Figs 2 and 3).

The OT mRNA level in the SON increased by more than 50% after infusion of HA, 2-TEA or 4-MeHA (Fig. 4; $P < 0.01$).

Experiment 2: effect of selective H_1 - or H_2 -receptor blockade on basal and HA-induced CRH, AVP and OT mRNA in the hypothalamic PVN and SON

Except for a slight inhibitory effect of the H_2 -receptor antagonist CIM on basal CRH mRNA levels (Fig. 1;

$P < 0.05$), treatment with the H_1 -receptor antagonist MEP or CIM had no effect on basal expression of CRH, AVP and OT mRNA in the PVN and/or SON.

HA-induced CRH expression was not significantly affected by MEP or CIM (Fig. 1). When MEP was administered before HA, which on its own had no stimulatory effect upon AVP mRNA expression, a lower level of AVP mRNA was observed in the PVN and SON (Figs 2 and 3; $P < 0.05$). Pretreatment with CIM did not have this effect (Figs 2 and 3). Both MEP and CIM inhibited the HA-induced rise in OT mRNA levels (Fig. 4; $P < 0.01$).

Discussion

We found that centrally administered HA increased the level of CRH mRNA in the PVN, indicating that HA may have a role as a central stimulatory neurotransmitter activating CRH neurons. In accordance with this, we have previously found that HA induces expression of *c-fos*, an indicator of early neuronal activation (27, 28), in CRH-immunoreactive neurons of the PVN (13). The effect seems to be caused by H_1 - and H_2 -receptor activation since administration of an H_1 - as well as an

Figure 2 Effect of HA, HA agonists or HA antagonists on AVP mRNA in the PVN. At time 0 min, rats were decapitated and *in situ* hybridization histochemical analysis of AVP mRNA performed. For further details, see the legend to Fig. 1. # $P < 0.05$ vs Sa + HA.

Figure 3 Effect of HA, HA agonists or HA antagonists on AVP mRNA in the SON. At time 0 min, rats were decapitated and *in situ* hybridization histochemical analysis of AVP mRNA performed. For further details, see the legend to Fig. 1 # $P < 0.05$ vs Sa + HA.

H₂-receptor agonist stimulated the expression of CRH mRNA. The CRH neurons in the PVN mainly project to the external layer of the median eminence where they release CRH into the pituitary portal blood. The present data are therefore in accordance with our previous findings that H₁- and H₂-receptor activation by the same agonists, as used here and in similar doses, stimulated CRH release into the long pituitary portal vessels in anesthetized rats (16). It is therefore likely that the previously demonstrated stimulatory effect of H₁- and H₂-receptor agonists on ACTH and β -endorphin secretion (16, 23) is mediated at least in part by activation of CRH neurons. In support of this hypothesis, the agonist-induced ACTH and β -endorphin secretion was inhibited by immunoneutralization of endogenous CRH (16). H₂-receptor blockade by CIM inhibited slightly basal expression of CRH mRNA whereas H₁-receptor blockade had no such effect. This may indicate the existence of a basal H₂-receptor-mediated histaminergic tone on CRH synthesis. However, this effect is not important for basal ACTH and β -endorphin secretion since CIM did not influence basal secretion of these hormones (23). Neither the H₁- nor the H₂-receptor antagonist inhibited the HA-induced increase in CRH

mRNA. We have no obvious explanation for this somewhat surprising observation, but the changes in CRH mRNA levels were small and the risk of type II error significant, i.e. there may have been differences that we could not detect. However, another explanation could be that blockade of both receptors is necessary to obtain inhibition of the HA-induced increase in CRH mRNA. Also in contrast to the present results is the inhibitory effect of MEP and CIM on HA-induced ACTH and β -endorphin secretion (23). However, this could be due to the fact that release may take place without changes in CRH synthesis as these are not necessarily coupled (A G Watts, personal communication), and that the synergistic effects between CRH and AVP/OT allows for small simultaneous changes in CRH and AVP/OT to cause greater changes in ACTH and β -endorphin levels.

The present finding that HA or selective H₁- and H₂-receptor agonists did not affect AVP mRNA levels in the PVN or SON is in contrast with our previous observations that AVP mRNA increased a little in the PVN in response to HA (14). However, the difference found in the previous study (14) was small and we may very well have overlooked a minor effect in the present

Figure 4 Effect of HA, HA agonists or HA antagonists on expression of OT mRNA in the SON. At time 0 min, rats were decapitated and *in situ* hybridization histochemical analysis of OT mRNA performed. For further details, see the legend to Fig. 1. ** $P < 0.01$ vs Sa + Sa; ## $P < 0.01$ vs Sa + HA.

experiment (statistical type II error). Indeed, there is a slight tendency of an H_1 - and H_2 -receptor-mediated stimulation in the PVN but not in the SON. However, we cannot rule out the possibility that the previously found effect was an accidental finding. Furthermore, since we cannot discriminate between parvo- and magno-cellular neurons and since the signal from parvocellular neurons is overshadowed by that from magnocellular ones, a significant increase in AVP mRNA in parvocellular neurons may very well have taken place.

The basal expression of AVP mRNA was unaffected by H_1 - or H_2 -receptor blockade, indicating the lack of basal histaminergic tone on AVP synthesis. In accordance with this, we previously found that basal AVP mRNA expression was unaffected by HA synthesis (29). In contrast, blockade of the histaminergic system may inhibit AVP mRNA levels when the vasopressinergic system is activated. This is supported by our observation that blockade of HA synthesis during dehydration attenuated the increase in AVP mRNA (29). Both H_1 - and H_2 -receptor activation causes release of AVP (17), but as seen in the present study not to an extent where synthesis is stimulated. This is probably due to the short duration of the histaminergic stimuli and the small fractional amount of stored AVP being released in response to the stimulation. However, using intronic probes might have demonstrated expression of AVP. The fact that centrally administered HA induced expression of *c-fos* in AVP-immunoreactive neurons of the PVN and SON (13) indicates that AVP neurons can be activated by HA. In support of this are recent observations of the ability of HA to depolarize AVP neurons in the SON probably via an H_1 -receptor mechanism (30).

The inhibitory effect of combined MEP and HA administration on mRNA levels of AVP in the PVN and SON is difficult to explain. The combination of MEP and HA should be equivalent to H_2 -receptor activation but the result was different from that observed with 4-MeHA alone.

The stimulatory effect of HA on ACTH/ β -endorphin and prolactin secretion is in part mediated via AVP (21, 22) and exerted via V_1 and V_2 receptors (31, 32). On this basis, it is surprising that histaminergic activation has no effect on AVP mRNA levels. However, as mentioned for CRH, small changes in AVP may in synergy with changes in CRH lead to significant effects on ACTH and β -endorphin secretion. Furthermore, the role of AVP in HA-induced secretion of ACTH, β -endorphin and prolactin is in part permissive (33, 34), and does not involve changes in AVP secretion and thereby in synthesis.

In accordance with our previous experiments (14), we found that HA strongly stimulated expression of OT mRNA in the SON. Together with a previous study where we found that HA induced *c-fos* expression in OT-immunoreactive neurons of the SON and PVN (13), this indicates that HA activates oxytocinergic neurons.

The effect of HA on OT mRNA seems to be mediated via activation of both H_1 and H_2 receptors since the effect was blocked by selective blockade of H_1 or H_2 receptors. In accordance with this, both the H_1 - and H_2 -receptor agonists increased the expression of OT mRNA. We have previously found that OT release into peripheral plasma is stimulated by both H_1 - and H_2 -receptor activation (15), whereas HA has no effect upon release of OT into pituitary portal blood (16), indicating that mainly magnocellular OT neurons of the hypothalamo-neurohypophyseal system are activated by HA. Electrophysiological studies have demonstrated that HA has either no effect (30), or an inhibitory one probably via an H_2 -receptor mechanism, on OT neurons in the SON (35). A possible explanation for the discrepant results is that the stimulatory effect found is exerted via HA receptors located on interneurons, whereas the electrophysiological studies investigated the direct effect of HA on OT neurons.

In summary, we found that HA as well as an H_1 - or H_2 -receptor agonist stimulated expression of CRH and OT mRNA in the PVN and SON respectively. In contrast, HA or the H_1 - or H_2 -receptor agonist had no effect on AVP mRNA levels in the PVN or SON. Pretreatment with H_1 - or H_2 -receptor antagonists inhibited the HA-induced increase in OT mRNA levels but had no effect on the HA-induced increase in CRH mRNA levels.

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